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ORIGINAL PAPER

A pooled analysis of 12 cohort studies of dietary fat, cholesterol and egg intake and ovarian cancer

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Abstract Fat and cholesterol are theorized to promote ovarian carcinogenesis by increasing circulating estrogen levels. Although case–control studies have reported positive associations between total and saturated fat intake and ovarian cancer risk, two cohort studies have observed null associations. Dietary cholesterol and eggs have been positively associated with ovarian cancer risk. A pooled analysis was conducted on 12 cohort studies. Among 523,217 women, 2,132 incident epithelial ovarian cancer cases were identified. Study-specific relative risks (RR) and 95% confidence intervals (CI) were calculated by Cox proportional hazards models, and then pooled using a random effects model. Total fat intake was not associated with ovarian cancer risk (pooled multivariate RR = 1.08, 95% CI 0.86–1.34 comparing ≥45 to 30–<35% of calories). No association was observed for monounsaturated, polyunsaturated, trans-unsaturated, animal and vegetable fat, cholesterol and egg intakes with ovarian cancer risk. A weakly positive, but non-linear association, was observed for saturated fat intake (pooled multivariate RR = 1.29, 95% CI: 1.01–1.66 comparing highest versus lowest decile). Results for histologic subtypes were similar. Overall, fat, cholesterol and egg intakes were not associated with ovarian cancer risk. The positive association for saturated fat intake at very high intakes merits further investigation.

Keywords Diet · Fat · Cholesterol · Egg · Ovarian cancer

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Introduction

Total, animal and saturated fat have been hypothesized to promote the development of ovarian cancer. Ecological studies have shown high correlations between total fat ($r > 0.67$) [1, 2], particularly animal fat (r=0.78) [1], and ovarian cancer mortality. In a regression analysis based on 21 countries, a 50% reduction in fat intake from current levels was associated with a projected 40% lower relative risk of ovarian cancer for women aged 30–69 years old [3].

Most [4–9], but not all [10–13] case–control studies have reported positive associations between total, saturated and animal fat intake and ovarian cancer risk. In contrast, two cohort studies have observed no associations [14, 15] with total, saturated and animal fat. Furthermore, one case–control study found a higher risk of mucinous ovarian cancer with higher intake of saturated fat, while there was no association present for non-mucinous tumors [6]. In the few studies that have reported an association, higher intakes of cholesterol and eggs generally have been associated with a higher risk of ovarian cancer [6, 14–19].

Due to the potential for recall bias to influence observed diet and cancer associations in case–control studies, further prospective assessment of these associations is needed. We investigated the associations between intakes of fat, cholesterol and eggs and risk of ovarian cancer in a pooled analysis of 12 cohort studies [14, 15, 20–29]. Given that the effect of fat, cholesterol and eggs may vary by risk factors for ovarian cancer, we also considered whether these associations differed by body mass index, parity, oral contraceptive use, postmenopausal hormone use and menopausal status. Additionally, since particular histological subtypes of ovarian cancer resemble different gynecological tissue [30], behave different clinically [31], and may have genetic differences [31], individual histological subtypes may be associated with different etiologies. Thus, we examined associations between intakes of fat separately with endometrioid, mucinous and serous ovarian cancers.

Material and methods

Population

A pooled analysis of the primary data from 12 prospective cohort studies [14, 15, 20–29] based in North America and Western Europe was conducted in The Pooling Project of Prospective Studies of Diet and Cancer (Table 1). To be included in the ovarian cancer analyses, each study needed a minimum of 50 incident ovarian cancer cases, an assessment of usual food and nutrient intake and validation of the dietary assessment tool or a closely related instrument. Each study sent to the Harvard School of Public Health their primary data on intakes of specific nutrients and foods, nondietary factors, and cancer incidence and mortality outcomes. We inspected the data for completeness and resolved inconsistencies with the investigators of each study. Additionally, we checked to see that our study-specific analyses closely reproduced original publications.

Two of these studies, the Canadian National Breast Screening Study and Netherlands Cohort Study were analyzed as case–cohort studies, because the investigators of these two studies each selected a random sample of the cohort to provide the person time data for the cohort and have processed questionnaires for only this random sample and the incident cancer cases. The follow-up of the Nurses' Health Study was divided into two sections where part A followed individuals from the completion of the 1980 food frequency questionnaire to 1986, and part B followed individuals from the completion of the 1986 food frequency questionnaire to 2002. On the basis of the underlying theory of survival data, blocks of person-time in different time periods are asymptotically uncorrelated,

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Table 1 Daily median intakes of fat, cholesterol and eggs by cohort study in the ovarian cancer analyses in the Pooling Project of Prospective Studies of Diet and Cancer

Cohort[a]	Follow-up Years	Baseline Cohort Size[b]	Number of Cases	Mean Time to Diagnosis(SD)	Median (Interquartile Range)[c,d,e]								
					TFAT	SFAT	MFAT	PFAT	TrFAT	AFAT	VFAT	Cholesterol	Eggs[f]
AHS	1976–1988	18,402	53	5 (4)	37 (35–39)	11 (10–13)	13 (12–14)	9 (8–10)	–	12 (10–16)	22 (20–24)	173 (139–223)	11 (3–11)
BCDDP	1987–1999	32,885	142	4 (3)	35 (29–41)	12 (9–14)	12 (10–14)	7 (5–9)	–	–	–	222 (170–287)	7 (2–14)
CNBSS[g]	1980–2000	49,613	223	10 (5)	43 (39–47)	17 (15–19)	16 (15–18)	5 (4–6)	–	30 (26–35)	12 (9–15)	305 (266–352)	21 (14–29)
CPS II	1992–2001	61,202	278	4 (2)	34 (27–40)	11 (8–13)	12 (10–15)	6 (5–8)	–	–	–	182 (143–232)	7 (2–14)
IWHS	1986–2001	28,486	208	8 (5)	34 (30–38)	12 (10–14)	13 (11–14)	6 (5–7)	2 (1–2)	19 (16–23)	14 (11–17)	255 (206–310)	7 (7–22)
NLCS[g]	1986–1995	62,412	208	5 (2)	39 (36–43)	15 (14–18)	14 (13–16)	7 (5–10)	–	28 (23–33)	11 (5–16)	226 (190–264)	14 (7–21)
NYSC	1980–1987	22,550	77	4 (2)	34 (32–37)	12 (11–13)	11 (10–12)	5 (5–6)	–	25 (22–28)	9 (8–11)	315 (269–372)	–
NYU	1985–1998	12,401	65	6 (3)	41 (36–45)	16 (14–18)	14 (12–15)	6 (5–7)	–	21 (17–26)	19 (14–23)	275 (219–347)	14 (7–29)
NHS(a)	1980–1986	80,195	120	3 (2)	39 (34–44)	16 (13–18)	16 (13–19)	5 (4–6)	2 (2–3)	29 (23–35)	9 (6–13)	322 (262–387)	22 (7–22)
NHS(b)	1986–2002	59,538	315	9 (4)	33 (29–36)	12 (10–13)	12 (10–14)	6 (5–7)	1 (1–2)	18 (15–21)	14 (11–17)	236 (195–280)	7 (7–22)
NHS II	1991–2000	91,502	52	4 (3)	32 (28–35)	11 (10–13)	12 (10–14)	5 (5–6)	2 (1–2)	17 (14–20)	14 (11–16)	212 (178–251)	7 (4–22)
SMC	1987–2004	61,103	287	8 (4)	30 (27–34)	13 (11–15)	11 (10–13)	4 (4–5)	–	–	–	210 (180–243)	6 (3–13)
WHS	1993–2004	32,466	104	5 (3)	30 (26–34)	10 (9–12)	11 (9–13)	6 (5–7)	1 (1–1)	16 (13–19)	13 (11– 16)	204 (168–246)	7 (4–22)

[a] AHS = Adventist Health Study, BCDDP = Breast Cancer Detection Demonstration Project Follow-up Study, CNBSS = Canadian National Breast Screening Study, CPS II = Cancer Prevention Study II Nutrition Cohort, IWHS = Iowa Women's Health Study, NLCS = Netherlands Cohort Study, NYSC = New York State Cohort, NYU = New York University Women's Health Study, NHS(a) = Nurses' Health Study (part a), NHS(b) = Nurses' Health Study (part b), NHS II = Nurses' Health Study II, SMC = Swedish Mammography Cohort, WHS = Women's Health Study

[b] Baseline cohort size determined after specific exclusions (i.e., prior cancer diagnosis other than non-melanoma skin cancer at baseline, bilateral oophorectomy prior to baseline, or $\log_e$-transformed energy intakes beyond three standard deviations from the study-specific $\log_e$-transformed mean energy intake of the population)

[c] Median intakes of TFAT, total fat; SFAT, saturated fat; MFAT, monounsaturated fat; PFAT, polyunsaturated fat; TrFAT, trans-unsaturated fat; AFAT, animal fat; VFAT, vegetable fat are based on percent of calories from that particular fat

[d] Cholesterol and egg medians are based on daily milligram and gram intakes, respectively

[e] Studies which have a – did not estimate that nutrient or did not ask on their questionnaire about the consumption of that food item

[f] 50 g is the approximate weight of 1 egg

[g] The Canadian National Breast Screening Study and the Netherlands Cohort Study are analyzed as case–cohort studies so the baseline cohort size does not reflect the above exclusions

regardless of the extent to which they are derived from the same people [32]. Thus, pooling estimates from these two time periods, and the cases that arise within them, produces estimates and estimated standard errors that are as valid as those from a single period. The methods have been described in detail elsewhere [33].

Exclusions

In addition to applying the exclusions that each study had predefined for their cohort, we excluded individuals if they had a prior cancer diagnosis other than non-melanoma skin cancer at baseline, had a bilateral oophorectomy prior to baseline, or if they had $\log_e$-transformed energy intakes beyond three standard deviations from the study-specific $\log_e$-transformed mean energy intake of their respective population. The Adventist Health Study [20] and New York State Cohort [25] did not obtain information on oophorectomy at baseline, and thus we were not able to exclude individuals who had a bilateral oophorectomy prior to baseline in these studies.

Exposure assessment

Usual frequency of consumption of foods and nutrients was estimated at baseline from the study-specific food frequency questionnaires (FFQ) [33]. All studies provided data on intake of total, saturated, monounsaturated, and polyunsaturated fat and cholesterol. The polyunsaturated fat intake data corresponded to linoleic acid consumption for the Adventist Health Study, the Breast Cancer Detection Demonstration Project Follow-up Study, the Cancer Prevention Study II Nutrition Cohort and the New York University Women's Health Study and to total polyunsaturated fat consumption for the remaining studies. Animal and vegetable fat intake was estimated in nine cohort studies and four cohort studies measured trans-unsaturated fat consumption (see Table 1). Most studies estimated nutrient intakes using the food composition method [34], but the New York State Cohort used the ''regression weight'' method to estimate nutrient values [25]. The regression-residual method [34] was used to adjust nutrient intakes to an energy intake of 1600 kcal/day. All studies, except for the New York State Cohort, measured consumption of eggs. Egg intake was analyzed in gram units to take into account differences in portion sizes on the study-specific questionnaires.

Energy-adjusted correlations between measurement of fat, cholesterol and egg intake from the study-specific FFQ or a closely related instrument and multiple 24 hour recalls or food records ranged from 0.44 to 0.62 for total fat [34–41], 0.42–0.66 for saturated fat [34, 36–41], 0.51–0.62 for monounsaturated fat [34, 37, 39, 41], 0.22–0.75 for polyunsaturated fat [34, 36, 37, 39–41], 0.21–0.61 for cholesterol [34–41] and 0.61–0.64 for egg intake [40, 42]. Most of these correlations had been de-attenuated [34, 35, 37–40] to account for day to day variation in intake.

Information on non-dietary factors was collected on the baseline self-administered questionnaires within each individual study. The majority of studies obtained information on multiple reproductive factors, body mass index, smoking status, and physical activity.

Outcome assessment

Participants were followed from the date of the baseline questionnaire until date of diagnosis of ovarian cancer, date of death, date the participant moved out of the study area (if applicable), or end of follow-up, whichever came first. Invasive epithelial ovarian cancer was ascertained by self-report with subsequent medical record review [14, 27, 43], cancer registry linkage [15, 22, 24, 25, 28] or both [20, 21, 23, 44]. Some studies also obtained incident outcome and/or mortality information from death registries [14, 15, 21, 23, 25, 27, 29, 43, 44]. Invasive epithelial ovarian cancer was defined by ICD-9 code 183.0 or ICD-10 code C56. Borderline and non-epithelial ovarian cancer cases, as determined by International Classification of Diseases for Oncology morphology codes [45] or the histological information supplied by individual studies, were not included as cases.

Statistical analysis

We analyzed associations for intakes of total fat and each type of fat as a percent of total calories in separate nutrient density models. In this model, because we also adjusted for total calories, the coefficient for each type of fat can be interpreted as the effect of an increase in the percent of total calories from the particular type of fat compared to an identical decrease in the percent of total calories from all other sources of total calories. For each study, we corrected the relative risk for total, saturated, monounsaturated, and polyunsaturated fat for measurement error using the regression coefficients between fat intakes estimated by the food frequency questionnaires and by the reference methods that were either multiple diet records or 24 hour recalls [46, 47]. We did not calculate measurement error-corrected relative risks for animal, vegetable and trans-unsaturated fats because intakes of these fat subtypes were not calculated for the reference method in several studies.

We also conducted analyses using the multivariate nutrient density model in which, together with total caloric intake, protein, alcohol, saturated fat, monounsaturated fat,

and polyunsaturated fat intakes were specified in the same model as a percent of total calories [34]. We controlled for total energy intake, because the range of energy intake to maintain energy balance is relatively narrow for an individual. In this multivariate nutrient density model, the coefficient for each type of fat can be interpreted as the effect of an increase in the percent of total caloric intake from the particular type of fat compared to an identical decrease in the percent of total calories from carbohydrates. Similar analyses were conducted with intakes of animal and vegetable fat.

Using the partition model, analyses were conducted that simultaneously adjusted for intakes of saturated fat, monounsaturated fat, polyunsaturated fat and nonfat calories [48]. In this partition model, the coefficient for each type of fat can be interpreted as the effect of an increase in the intake from the particular type of fat, because energy intake is not held constant. Finally, analyses were conducted using the energy adjusted estimates of intake of total fat and fat subtypes in g/day in the model.

Dietary exposures were modeled either (1) categorically according to quantiles (i.e., quartiles, deciles) defined within each individual study or study-wide absolute intake cutpoints and or (2) continuously. Studies were excluded from the analysis of a particular dietary factor if they did not measure intake of that specific dietary exposure or if that item was not consumed in that population.

Relative risks and 95% confidence intervals were calculated by Cox proportional hazards models for each individual study. To test whether there was a linear trend in the risk of disease with increasing intake, a continuous variable with values corresponding to the median value for each exposure category was included in the model, the coefficient for that variable was evaluated using the Wald test. SAS software [49] was used for the cohort analyses, and Epicure software [50] was used for case–cohort analyses of Canadian National Breast Screening Study [22] and Netherlands Cohort Study [24].

Study-specific relative risks were pooled using a random effects model [51]. Between-studies heterogeneity was calculated using the Q statistic [51, 52]. The models included stratification by age at baseline (in years) and the year the baseline questionnaire was returned and treated follow-up time as the time scale. Thus, this analytic strategy resulted in a time metric that simultaneously accounted for age, calendar time and time since entry into the study. Multivariate relative risks were adjusted for age at menarche, menopausal status at baseline, oral contraceptive use, hormone replacement therapy use among postmenopausal women, parity, body mass index, smoking status, physical activity, and energy intake, modeled identically across studies. An indicator variable for missing values was also generated within a study for each measured covariate, if applicable.

We also evaluated whether fat and cholesterol intake was linearly associated with ovarian cancer risk by comparing nonparametric regression curves using restricted cubic splines to the linear model using the likelihood ratio test, and by visual inspection of the restricted cubic spline graphs [53, 54]. The studies were combined into a single data set, and analyzed as above, additionally stratified by study.

Further analyses were conducted to examine effect modification by age at diagnosis, body mass index, parity, oral contraceptive use, postmenopausal hormone replacement therapy use, and menopausal status at diagnosis. Because most studies collected information at baseline only, for analyses evaluating whether menopausal status modified the association between each type of fat and ovarian cancer risk, we assigned menopausal status at follow-up in each study using an algorithm based on an analysis of 42,531 Nurses' Health Study participants who were premenopausal in 1976 and remained premenopausal or had natural menopause by 1992 [55]. Women who were premenopausal at baseline and whose age at follow-up was ≤51 years were considered to be premenopausal, between 51 and 55 years were considered as having an uncertain menopausal status and ≥55 years were considered to be postmenopausal. Using a metaregression model, we tested for variation in relative risks by postmenopausal hormone replacement therapy use, parity and age at diagnosis [56]. For the remaining potential modifying factors, a cross-product term of the ordinal score for the level of each factor and intake of a specific type of fat expressed as a continuous variable was included in the nutrient density model. Participants with missing values of the modifying factor of interest were excluded from these analyses. Separate analyses were conducted for endometrioid, mucinous and serous subtypes among those studies having more than 10 cases of the specific histological subtype. Subtype analyses were conducted among these three histologies since they are the three most common histologies and represented 68% of all ovarian cancer cases in our population. We tested whether results differed across the subtypes using a contrast test [57].

Results

Table 1 presents the study-specific characteristics and daily median intakes of total fat, types of fat, cholesterol and eggs. The total study population consisted of 553,217 women, among whom 2,132 developed invasive epithelial ovarian cancer. Studies had a maximum follow-up time

ranging from 7 years in the New York State Cohort to 22 years in the Nurses' Health Study. The mean time to diagnosis of ovarian cancer was shortest among cases in the Nurses' Health Study part (a) (mean = 3 years) and greatest among cases in the Canadian National Breast Screening Study (mean = 10 years). Daily median total fat intake ranged from 30% of calories in the Swedish Mammography Cohort and Women's Health Study to 43% of calories in the Canadian National Breast Screening Study. As expected, since the Adventist Health Study had a high proportion of vegetarians, the Adventist Health Study had the lowest median intake of animal fat and cholesterol and the highest median intake of vegetable fat compared to all other studies.

Total fat intake was not associated with the risk of ovarian cancer (pooled multivariate RR = 1.08, 95% CI: 0.86–1.34) when comparing intakes of greater than 45% of calories from fat to 30–<35% of calories from fat (Figure 1). For this same comparison and the continuous model, there was no heterogeneity present between studies (p value for test of between studies heterogeneity >0.45) and the majority of studies had relative risk estimates close to the null (Figure 2). In addition, there was no evidence that low intakes of total fat lowered ovarian cancer risk when comparing intakes of less than 25% of calories from fat to 30–<35% of calories from fat.

When intake of each fat was modeled using study-specific quartiles (Table 2) or continuously (Table 3), no statistically significant associations were observed between intakes of total fat and types of fat (saturated, monounsaturated, polyunsaturated, trans-unsaturated, animal and vegetable) and risk of ovarian cancer, although the weak positive associations for animal and saturated fat were marginally significant. When examining more extreme contrasts, comparing the highest to lowest decile, slight positive associations between animal (pooled multivariate RR = 1.23, 95% CI: 0.98–1.55, p value, test for trend = 0.12) and saturated fat (pooled multivariate RR = 1.29 95% CI: 1.01–1.66, p value, test for trend = 0.21) and ovarian cancer risk also were observed, although no dose–response was apparent. When evaluating whether intake of each fat was linearly associated with ovarian cancer risk by conducting restricted cubic spline analyses, we found a non-linear association only for saturated fat (p value, test for nonlinearity = 0.05). A higher risk of ovarian cancer was restricted to intakes greater than 21% of calories from saturated fat. Likewise, no statistically significant association with ovarian cancer risk was observed for cholesterol intake. Results of the association between energy adjusted intakes of fat and types of fat and ovarian cancer risk were similar to the continuous and quartile results presented (data not shown). Results were similar between age-adjusted and multivariate-adjusted models. Although there were no statistically significant differences in the risk estimates observed for endometrioid, mucinous and serous ovarian cancer for each dietary factor, the risk of serous ovarian cancer increased with higher intake of saturated fat (pooled multivariate RR for 5% calories of saturated fat per day = 1.12, 95% CI: 1.01–1.25).

Pooled age and energy-adjusted relative risks corrected for measurement error for an increment of 5% of energy were 1.01 (95% CI: 0.93–1.09; p-value, test for heterogeneity = 0.63) for total fat; 1.14 (95% CI: 0.94–1.38; p-value, test for heterogeneity = 0.26) for saturated fat; 1.02 (95% CI: 0.82–1.28; p-value, test for heterogeneity = 0.68) for monounsaturated fat and 0.82 (95% CI: 0.62–1.10; p-value, test for heterogeneity = 0.97) for polyunsaturated fat.

Using the multivariate nutrient density model approach, total calories and the percent of total calories from saturated fat, monounsaturated fat, polyunsaturated fat, alcohol and protein intakes were included simultaneously in the analysis as continuous variables (relative risk estimates expressed as an increment of 5% of total calories). When substituted for an equivalent reduction in carbohydrate consumption, no association with ovarian cancer risk was observed for an increase in saturated fat (pooled multivariate RR = 1.06, 95% CI: 0.91–1.22), monounsaturated fat (pooled multivariate RR = 1.00, 95% CI: 0.86–1.17) and polyunsaturated fat (pooled multivariate RR = 0.98, 95% CI: 0.84–1.44). Similarly, no association was seen for animal fat (pooled multivariate RR = 1.03, 95% CI: 0.96–1.11) and vegetable fat (pooled multivariate RR = 0.98, 95% CI: 0.92–1.05) when substituted for an equivalent reduction in carbohydrate consumption.

In analyses that simultaneously adjusted for intakes of saturated fat, monounsaturated fat, polyunsaturated fat and nonfat calories as continuous variables (increment = 45 calories/day, which is equivalent to the amount of calories for an increase of 5% of total calories from fat) (the partition model), we found no association for saturated fat (pooled multivariate RR = 1.04, 95% CI: 0.97–1.10), monounsaturated fat (pooled multivariate RR = 1.01, 95% CI: 0.93–1.10) and polyunsaturated fat (pooled multivariate RR = 0.98, 95% CI: 0.99–1.01) and risk of ovarian cancer. Likewise, in analyses that simultaneously adjusted for intakes of animal fat and vegetable fat, no association for animal fat (pooled multivariate RR for 5% of calories of animal fat per day = 1.01, 95% CI: 1.00–1.03) and vegetable fat (pooled multivariate RR for 5% of calories of vegetable fat per day = 1.00, 95% CI: 0.98–1.03) and ovarian cancer risk was observed (data not shown).

Egg consumption was not associated with ovarian cancer risk (pooled multivariate RR = 1.18, 95% CI: 0.89–1.57, p-value, test for trend = 0.52, p-value for test of between studies heterogeneity = 0.87, comparing intake of >50 g/day of eggs to <6.25 g/day of eggs). When examined continuously, higher intakes of eggs were associated with a

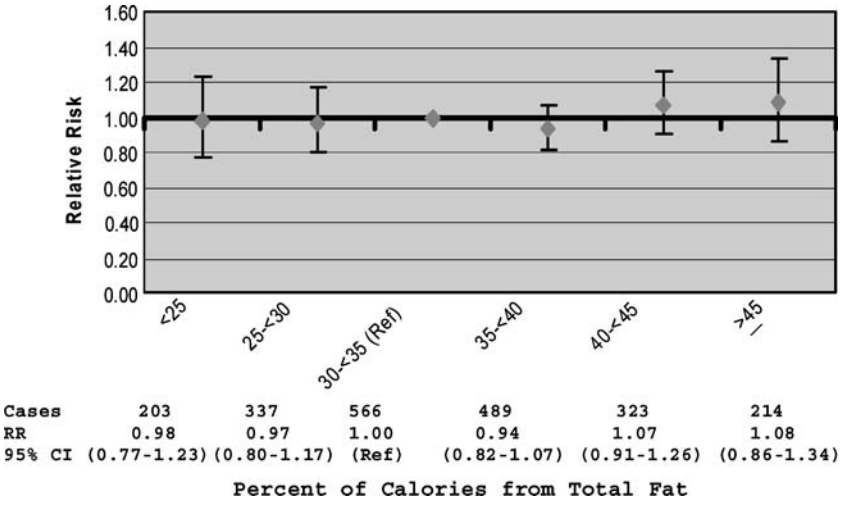

Fig. 1 Pooled multivariate adjusted (a–f) relative risks (RR) and 95% confidence intervals (CI) for ovarian cancer according to percent of calories from total fat. (a) Multivariate relative risks were adjusted for age at menarche (< 13, 13, >13 years), menopausal status at baseline (premenopausal, postmenopausal), oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), body mass index (< 23, 23–< 25, 25–< 30, ≥30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuous). (b) CNBSS and NYU were not included in the < 25 category because they did not have any cases in that category. The participants who were not cases who would have been in this lowest category were included in the next lowest category (25–< 30). (c) AHS was not included in the < 25 and 25–< 30 categories because they did not have any cases in these categories (d) NHS II and WHS were not included in the ≥45 category because they did not have any cases in that category. The participants who were not cases who would have been in this highest category were included in the next highest category (40–< 45). (e) *p*-Value, test for trend=0.81 (f) *p*-Value, test for between-studies heterogeneity for ≥45% of calories from total fat category = 0.73

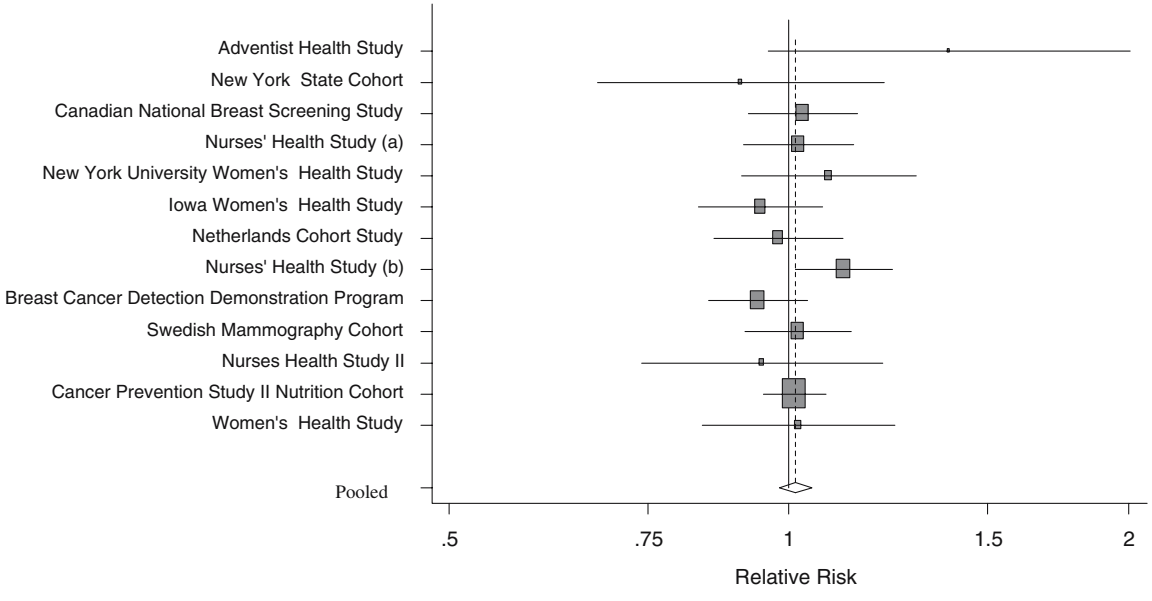

Fig. 2 Multivariate (a–c) adjusted relative risks (RR) and 95% confidence intervals (CI) for ovarian cancer according to percent of calories from total fat (5% of total caloric increase) by study. (a) Multivariate relative risks were adjusted for age at menarche (< 13, 13, >13 years), menopausal status at baseline (premenopausal, postmenopausal), oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), body mass index (< 23, 23–< 25, 25–< 30, ≥ 30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuous). (b) *p*-Value, test for between-studies heterogeneity = 0.45. (c) The black squares and horizontal lines correspond to the study-specific relative risks and 95% confidence intervals, respectively for a 5% of total calories increase from fat. The area of the black squares is proportional to the inverse of the sum of the between-studies variance, which is related to the sample size, the total number of cases, and the range of the variation in intake. The diamond represents the pooled multivariate relative risk and the 95% confidence interval. The vertical dashed line represents the pooled multivariate relative risk

Table 2 Pooled multivariate relative risks and 95% confidence intervals of ovarian cancer according to quartiles of fat and dietary cholesterol intake

Nutrient		Quartiles				$p_{\text{Heterogeneity}}$[a]	p-trend[b]
		First	Second	Third	Fourth		
Total fat	Cases	536	544	524	528		
(% of total calories)	MV RR[c] (95% CI)	1.00 (Ref)	1.05 (0.87–1.26)	1.05 (0.88–1.25)	1.08 (0.94–1.24)	0.30	0.41
Saturated fat	Cases	529	563	487	553		
(% of total calories)	MV RR[c] (95% CI)	1.00 (Ref)	1.11 (0.97–1.27)	0.99 (0.86–1.13)	1.14 (0.97–1.34)	0.13	0.22
Monounsaturated fat	Cases	547	542	553	490		
(% of total calories)	MV RR[c] (95% CI)	1.00 (Ref)	1.06 (0.93–1.19)	1.08 (0.90–1.29)	0.98 (0.86–1.12)	0.84	0.83
Polyunsaturated fat	Cases	555	532	546	499		
(% of total calories)	MV RR[c] (95% CI)	1.00 (Ref)	0.99 (0.86–1.13)	1.00 (0.89–1.14)	0.94 (0.80–1.09)	0.18	0.29
Trans-unsaturated fat[d]	Cases	198	205	216	180		
(% of total calories)	MV RR[c] (95% CI)	1.00 (Ref)	1.03 (0.76–1.40)	1.15 (0.83–1.60)	1.04 (0.84–1.28)	0.44	0.66
Animal fat[e]	Cases	362	356	326	381		
(% of total calories)	MV RR[c] (95% CI)	1.00 (Ref)	1.04 (0.87–1.24)	0.98 (0.83–1.14)	1.15 (0.99–1.33)	0.64	0.15
Vegetable fat[e]	Cases	355	365	369	336		
(% of total calories)	MV RR[c] (95% CI)	1.00 (Ref)	1.08 (0.93–1.26)	1.10 (0.94–1.28)	1.01 (0.87–1.18)	0.52	>0.99
Cholesterol	Cases	548	518	530	536		
(mg/day)	MV RR[c] (95% CI)	1.00 (Ref)	1.01 (0.87–1.17)	1.05 (0.90–1.23)	1.05 (0.93–1.18)	0.84	0.53

[a] p-value for the test for heterogeneity between studies

[b] p-value, test for trend

[c] Multivariate relative risks were adjusted for age at menarche (<13, 13, >13 years), menopausal status at baseline (premenopausal, postmenopausal), oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), body mass index (<23, 23–<25, 25–<30, ≥30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuous)

[d] AHS, BCDDP, CNBSS, CPS II, NLCS, NYSC, NYU, SMC are not included in this analysis because they did not measure this nutrient

[e] BCDDP, CPS II, SMC were not included in the animal and vegetables fat analyses because they did not measure this nutrient

slightly higher risk of ovarian cancer (pooled multivariate RR for a 50 g/day increment = 1.11, 95% CI: 0.99–1.24). Similar associations were observed for endometrioid (pooled multivariate RR for a 50 g/day increment = 1.31, 95% CI: 0.87–1.98), mucinous (pooled multivariate RR for a 50 g/day increment = 1.12, 95% CI: 0.60–2.10) and serous (pooled multivariate RR for a 50 g/day increment = 1.12, 95% CI: 0.91–1.37) ovarian cancers.

The associations for total fat, types of fat, cholesterol and eggs (for eggs, data not shown) were not modified by menopausal status at diagnosis (postmenopausal and premenopausal), oral contraceptive use (never and ever), hormone replacement therapy use among postmenopausal women (never, past and current) (Table 4), age (greater than and equal to or less than 63 years of age, the median age at diagnosis among the ovarian cancer cases) (data not shown), parity (≤1, >1 live births) (data not shown) and body mass index (≤25 and >25 kg/m^2) (data not shown). Because elevated risk of saturated fat was limited to the highest decile, we also assessed this contrast when examining effect modification. There was no evidence of interaction for all modification factors (data not shown). Sensitivity analyses excluding cases diagnosed during the first 2 years of follow-up were conducted to determine if the risk estimates were affected by including cases with an early diagnosis who may have altered their diet. Estimates for each dietary factor were comparable to the overall estimates (data not shown). Results were similar when we limited analyses to the first 6 years of follow-up compared to 6 or more years of follow-up (data not shown).

Discussion

Greater intakes of total fat, animal fat, saturated fat, cholesterol and eggs have been hypothesized to increase the risk of ovarian cancer. A meta-analysis [58], which included seven case–control studies and one cohort study (Iowa Womens' Health Study) has reported a higher risk of ovarian cancer with higher intakes of total, saturated and animal fat. Similar associations have been observed in most other [5, 9], but not all case–control studies [10–12] conducted recently. Furthermore, three of five case–control studies have reported that higher intakes of cholesterol and eggs were associated with a higher risk of ovarian cancer [6, 16–19]. In this pooled analysis of 12 cohort studies that prospectively assessed diet, no statistically significant associations were observed for intakes of total fat, most fat subtypes, dietary cholesterol, eggs and risk of ovarian cancer. A statistically significant positive association was

Table 3 Pooled multivariate relative risks and 95% confidence intervals for histological subtypes of ovarian cancer, continuous model

	Increment[a]	All ovarian cancer		Endometrioid cancer[b]		Mucinous cancer[c]		Serous cancer[d]		*p*-value[e]
		Multivariate RR (95% CI)[f]	*p*-value[g]	Multivariate RR (95% CI)[f]	*p*-value[g]	Multivariate RR (95% CI)[f]	*p*-value[g]	Multivariate RR (95% CI)[f]	*p*-value[g]	
Total fat[h]	5%	1.01 (0.98–1.05)	0.45	1.01 (0.92–1.11)	0.52	0.97 (0.84–1.11)	0.92	1.03 (0.98–1.08)	0.72	0.55
Saturated fat[h]	5%	1.07 (0.97–1.18)	0.09	1.05 (0.84–1.31)	0.35	1.06 (0.79–1.41)	>0.99	1.12 (1.01–1.25)	0.91	0.87
Monounsaturated fat[h]	5%	1.02 (0.94–1.10)	0.61	1.02 (0.81–1.27)	0.55	0.91 (0.66–1.25)	0.58	1.07 (0.96–1.20)	0.46	0.58
Polyunsaturated fat[h]	5%	0.94 (0.85–1.05)	0.62	1.02 (0.70–1.48)	0.23	0.82 (0.52–1.30)	0.43	0.96 (0.82–1.13)	0.99	0.78
Animal fat[h,i]	5%	1.04 (0.99–1.08)	0.74	1.07 (0.93–1.23)	0.30	1.00 (0.86–1.16)	0.89	1.05 (0.99–1.12)	0.74	0.72
Vegetable fat[h,i]	5%	0.98 (0.93–1.04)	0.60	0.98 (0.81–1.18)	0.25	0.96 (0.78–1.17)	0.96	0.99 (0.92–1.07)	0.87	0.86
Cholesterol[h]	100 mg/d	1.03 (0.98–1.08)	0.81	1.02 (0.83–1.24)	0.10	1.04 (0.85–1.29)	0.66	1.05 (0.98–1.12)	0.79	0.97

[a] Increment for percent of calories from fat is based on a 5% increase in total calories and for cholesterol is based on the mean of the standard deviation of the mean intake

[b] Endometrioid analyses exclude AHS, NYSC and NYU due to small case numbers

[c] Mucinous analyses exclude AHS, BCDDP, NYSC, NYU, NHS II and WHS due to small case numbers

[d] Serous analyses exclude AHS due to small case numbers

[e] *p*-Value for the test for the common effect by histologic type (endometrioid, mucinous and serous)

[f] Multivariate relative risks were adjusted for age at menarche (<13, 13, >13 years), menopausal status at baseline (premenopausal, postmenopausal), oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), body mass index (<23, 23–<25, 25–<30, ≥30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuous)

[g] *p*-Value, test for between-studies heterogeneity

[h] Case numbers for total fat, saturated fat, monounsaturated fat, polyunsaturated fat and cholesterol intake (all = 2,132, endometrioid = 261, mucinous = 122, serous = 1,025) and animal fat and vegetable fat (all = 1,425, endometrioid = 167, mucinous = 89, serous = 711)

[i] BCDDP, CPS II, SMC were not included in the animal and vegetables fat analyses because they did not measure this nutrient

only observed for the highest decile of saturated fat and risk of ovarian cancer.

Higher intakes of total, animal and saturated fat have been theorized to promote ovarian carcinogenesis by an ability to cause higher levels of extragenital estrogen production [59]. Several [60–62], but not all [34, 63, 64], studies conducted, have shown a positive association between estrogens and fat intake.

Higher levels of estrogens, androgens and gonadotropins may help promote proliferation and malignant transformation of the ovarian epithelium, and thus, ovarian carcinogenesis [59, 65–68]. In contrast, progestins are hypothesized to decrease risk by mechanisms such as inducing apoptosis [21, 65, 66]. As seen in the Breast Cancer Detection Demonstration Project Follow-up Study, women, who took estrogen only replacement therapy but not estrogen–progestin only replacement therapy, were at a higher risk for ovarian cancer [21]. The majority of evidence linking sex steroid hormones to ovarian cancer risk has been indirect, through the strong, consistent inverse associations observed with oral contraceptive use and higher parity with ovarian cancer risk. However, the few prospective studies that have examined sex steroid hormones have shown that ovarian cancer risk was not associated with testosterone, DHEAS, estrone and SHBG levels [69, 70].

To date only one case–control study has examined dietary fat, cholesterol and egg intake in relation to risk of serous, mucinous and endometrioid ovarian cancers separately. This study found a higher risk of mucinous ovarian cancer with higher intake of saturated fat [12], while there was no association with serous ovarian cancer. In contrast, we saw no statistically significant difference in risk estimates by histology. No other statistically significant associations were observed in our analyses for serous, mucinous and endometrioid ovarian cancers. Due to the higher number of cases of serous histology compared to endometrioid and mucinous ovarian cancers, we had greater statistical power to assess this association. Due to the complexity of the disease and diagnosis at a late stage, potential misclassification could have occurred with regard to classifying cases according to histology; thus spurious results may be observed. However, the distribution of the cases according to the three histological types was similar to the percent distribution observed in registries and other studies for the main histological subtypes of ovarian cancer [71, 72].

Since our analyses were conducted using only a baseline FFQ, limitations of this analysis include that we were not able to assess changes in intake over time. Additionally, because we measured adult intake of fats,

Table 4 Pooled multivariate relative risks[a] and 95% confidence intervals of ovarian cancer for fat, types of fat, and cholesterol intake of ovarian cancer by menopausal status at diagnosis, oral contraceptive use and postmenopausal hormone use, continuous model

	Menopausal status at diagnosis[b–e]			Oral contraceptive use[e,f]			Postmenopausal hormone use[e,g,h,i]			
	Premenopausal	Postmenopausal	*p*-value	Never	Ever	*p*-value	Never	Past	Current	*p*-value
Total fat[j]	1.02 (0.90–1.15)	1.02 (0.97–1.07)	0.50[m]	1.02 (0.96–1.09)	1.00 (0.94–1.07)	0.76[m]	1.00 (0.91–1.09)	1.02 (0.92–1.12)	1.00 (0.91–1.09)	0.94[m]
Saturated fat[j]	1.01 (0.77–1.33)	1.11 (0.95–1.29)	0.42[m]	1.11 (0.95–1.28)	1.00 (0.86–1.17)	0.30[m]	1.07 (0.84–1.38)	1.06 (0.85–1.31)	1.07 (0.86–1.34)	0.81[m]
Monounsaturated fat[j]	0.97 (0.74–1.28)	1.03 (0.91–1.15)	0.18[m]	1.02 (0.90–1.15)	1.03 (0.90–1.19)	0.93[m]	0.98 (0.78–1.23)	1.05 (0.79–1.38)	0.99 (0.80–1.24)	0.98[m]
Polyunsaturated fat[j]	1.30 (0.82–2.07)	0.94 (0.83–1.05)	0.37[m]	0.94 (0.82–1.08)	1.05 (0.86–1.28)	0.44[m]	0.91 (0.77–1.07)	0.96 (0.64–1.45)	0.86 (0.64–1.17)	0.47[m]
Animal fat[j,k]	0.99 (0.88–1.12)	1.06 (1.00–1.12)	0.34[m]	1.06 (1.00–1.12)	1.01 (0.93–1.11)	0.55[m]	1.07 (0.99–1.16)	1.11 (0.95–1.30)	0.99 (0.82–1.18)	0.51[m]
Vegetable fat[j,k]	1.02 (0.87–1.19)	0.97 (0.91–1.03)	0.93[m]	0.96 (0.89–1.03)	1.03 (0.94–1.13)	0.39[m]	0.93 (0.86–1.02)	1.02 (0.85–1.23)	0.98 (0.79–1.23)	0.80[m]
Cholesterol[l]	0.97 (0.82–1.15)	1.03 (0.97–1.10)	0.62[m]	1.06 (1.00–1.13)	1.01 (0.92–1.10)	0.54[m]	1.05 (0.94–1.18)	0.99 (0.86–1.15)	1.07 (0.94–1.21)	0.77[m]

[a] Multivariate relative risks were adjusted for age at menarche (<13, 13, >13 years), menopausal status at diagnosis (premenopausal, postmenopausal), oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), body mass index (<23, 23–<25, 25–<30, ≥30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuous)

[b] NYSC was excluded from this analysis because they did not measure menopausal status on the baseline questionnaire

[c] AHS, BCDDP, CPS II, IWHS, NLCS, SMC and WHS were excluded from the premenopausal analysis due to small case numbers

[d] NHSII was excluded from the postmenopausal analysis due to small case numbers

[e] Case numbers for total fat, saturated fat, monounsaturated fat, polyunsaturated fat and cholesterol (premenopausal = 153, postmenopausal = 1399, never oral contraceptive use = 1178, ever oral contraceptive use = 608, never postmenopausal hormone use = 663, past postmenopausal hormone use = 251, current postmenopausal hormone use = 227), and animal fat and vegetable fat (premenopausal = 153, postmenopausal = 908, never oral contraceptive use = 808, ever oral contraceptive use = 465, never postmenopausal hormone use = 501, past postmenopausal hormone use = 143, current postmenopausal hormone use = 109)

[f] NYSC and NYU were excluded in the oral contraceptive use analysis because they did not measure oral contraceptive use on the baseline questionnaire

[g] CNBSS, NYSC, NYU and SMC were excluded from this analysis because they did not measure never, past or current postmenopausal hormone use on the baseline questionnaire

[h] NHS II was excluded from the never, past, current postmenopausal hormone use analysis due to small case numbers

[i] NLCS and NHS(a) were excluded from the current postmenopausal hormone use analysis due to small case numbers

[j] Increment for percent of calories from fat is based on a 5% increase in total calories

[k] BCDDP, CPS II, SMC were excluded in the animal and vegetables fat analyses because they did not measure this nutrient

[l] Increment for dietary cholesterol is based on a 100 mg/day increase

[m] *p*-Value, test for interaction

cholesterol and eggs, we may not have captured the relevant exposure time for ovarian cancer risk. It may be that dietary factors during a different life period (i.e., adolescence) may be the relevant exposure time to measure for ovarian cancer. Diet was measured prior to diagnosis of ovarian cancer; thus, a cancer diagnosis should not influence the reporting of fat, cholesterol and egg intake. However, women who were diagnosed with ovarian cancer close in time to the completion of the FFQ may have altered their diet due to prediagnostic disease signs and symptoms. To address whether inclusion of these early cases affects the risk estimates, sensitivity analyses excluding cases diagnosed during the first year and second year of follow-up were conducted to determine if the estimates were affected by including cases with an early diagnosis. Estimates from both models were comparable to the overall estimates. Thus, measurement errors in the intakes of these nutrients would result in non-differential misclassification, which would have tended to attenuate the relation between intakes of fat, cholesterol and egg intake with risk of ovarian cancer. However, the measurement error corrected risk estimates were similar to the uncorrected results.

Although, our categorization of covariates was limited by how each study asked the question, one of the advantages of our study was that we could control for covariates uniformly and classify the main exposures similarly, thereby removing potential sources of heterogeneity across studies. Within our models, we adjusted for most of the important known ovarian cancer risk factors if they were measured in a study. In studies that measured all of the covariates we included in our multivariate models, results from the age-adjusted and multivariate models were similar suggesting that residual confounding is small. Due to the inclusion of 12 cohort studies in North America and Europe, we had far greater statistical power than any of the individual cohort studies to examine whether associations differed for specific histological subtypes or population subgroups. Since the studies were conducted in a variety of populations with different dietary habits, we also could examine associations over a wide range of intakes.

In summary, we found no association between intakes of total fat, most fat subtypes, dietary cholesterol and eggs during adulthood and risk of ovarian cancer in this pooled analysis of 553,217 women. The positive association for saturated fat intake at very high intakes merits further investigation. We observed similar results for the relation between these dietary factors and ovarian cancer risk in histological subgroups. Associations of fat intake were not modified by main ovarian cancer risk factors, such as nulliparity, and preventive factors, such as oral contraceptive use.

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